

REMARKS

In the Office Action the Examiner repeated the rejections of claims 45-49 under 35 USC § 103(a) as being unpatentable over **Wassenaar** (U.S. Patent No. 7,060,289) in view of the Merck Manual. The Examiner observes that the Merck Manual teaches that athlete's foot, a fungus infection, commonly grows in warm moist areas between the toes. Further although **Wassenaar** does not teach a method for killing or inhibiting microorganisms including fungi, **Wassenaar** does disclose a single case study of a patient wherein excessive sweating of the forehead and groin resulted in a constant facial rash and chronic fungal infection of his groin. After **Wassenaar** used an alcoholic solution of anticholinergic amine to reduce the sweating, the facial rash and fungal groin infection improved. Therefore, the Examiner concludes that the combination of the Merck Manual (fungal infections develop in warm moist locations) with **Wassenaar** (excessive sweating may lead to fungal infections and reduction of such sweating causes improvement in the fungal infection) makes it obvious to use anticholinergic amines to inhibit and kill microorganisms including fungi.

Applicant respectfully traverses the Examiner's obviousness finding. The question here turns on what the **Wassenaar** disclosure would have suggested to one of ordinary skill in the art. Based primarily on Applicant's disclosure and to a lesser extent on the contents of the cited prior art, the area of art encompassing the instant invention would naturally include the art of topical antiseptics of the skin and methods and compositions that kill or inhibit bacteria, fungi and other skin pathogens. One of ordinary skill in this art would necessarily be familiar with any FDA monographs dealing with killing or controlling microorganisms on the skin. Applicant has attached a copy from the Federal Register of 21 CFR Parts 333 and 369 entitled "Tentative Final Monograph for OTC Healthcare Antiseptic Drug Products – June 17, 1994." The Examiner's attention is drawn to the table on page 3135 and the comments under section E (page 31411-31412). This document establishes the antiseptic efficacy of ethyl alcohol (60% to 95%).

Wassenaar (column 7-8) report experiments using cotton-polypropylene pads to apply glycopyrrolate topically. In column 7 experiments are presented to show that while alcoholic solutions in excess of 5% alcohol are effective, the most uniform distribution of glycopyrrolate occurs with a 66% solution of 95% alcohol. One of ordinary skill in the art would know that uniformity of active ingredient content from application to application is very important. In column 8 **Wassenaar** reports that using these pads to apply glycopyrrolate to a facial rash and fungal infection of the groin associated with excess sweating resulted in a decrease in the excessive sweating and a concomitant improvement in both the rash and the fungal infection. The Examiner concludes that this makes Applicant's discovery of using glycopyrrolate and similar ACQAs to kill bacteria and fungi obvious. The Examiner makes this finding by combining **Wassenaar** with information from the Merck Manual showing that fungal infections of the skin prefer moist locations. The reasoning seems to be that one of ordinary skill in the art knows that fungi prefer moist places and that the **Wassenaar** treatment resulted in a decrease in excessive sweating and a concomitant improvement in both a rash and fungal infection; therefore, it would be obvious to use glycopyrrolate to kill bacteria and fungi. Again, Applicant respectfully traverses this obviousness finding.

Applicant respectfully suggests that experiment reported by **Wassenaar** would suggest to one of ordinary skill in the art at least two different things. First, it would suggest that repeated treatments with antiseptic doses of alcohol would reduce populations of microorganisms on the skin which would thereby result in improvements of infections caused by those microorganisms. Second, it would suggest that reducing the availability of moisture (sweat) can lead less favorable growth conditions for microorganisms and to improvement in a facial rash and fungal groin infection caused by such microorganisms. It is also likely that one of ordinary skill in the art might consider that the first conclusion and the second conclusion could both contribute; first

use an antiseptic to reduce the microorganism population and then provide inferior (drier) growth conditions to keep the population reduced.

It would appear from the reference is that Wassenaar himself believed that the results were entirely due to the reduction of moisture; otherwise there would be no reason to include the addition of antifungal agents (column 7 at line 49). This is the teaching that one of ordinary skill in the art would have perceived. Absent a showing (as in the present application) of actual killing or inhibition of dermatophytic fungi, one of ordinary skill in the art would not interpret **Wassenaar** as showing or suggesting that glycopyrrolate was effective at killing and inhibiting bacteria and dermatophytic fungi. At the time of the invention ACQAs were not known to kill or inhibit either bacteria or fungi. It was known that moisture (excess sweat) could favor fungal infections of the skin. **Wassenaar** showed that reducing excess sweating by applying an antiseptic solution of glycopyrrolate resulted in improvement of a fungal infection of the skin. One of ordinary skill would have not expectation that glycopyrrolate application would have any effect on bacteria and fungi apart from the effect of the alcohol and the drier environment.

The **Wassenaar** experiment does not demonstrate or suggest that ACQAs (such as glycopyrrolate) kill and inhibit microorganisms including dermatophytic fungi. By "killing" one means that the compound has a direct toxic biological effect as opposed to an indirect environmental effect such as by altering the growth environment (i.e., making things drier). Applicant has made the hitherto unknown and unexpected discovery that ACQAs, including glycopyrrolate kill (D-value) and inhibit (MIC) fungi and bacteria in tests. Again the Examiner is directed to paragraphs [0057] to [0063] of the specification. It is known that anti-fungal agents are widely sought; Applicant is the first to recognize the anti-fungal properties of this class of compounds. Applicant also recognizes the association of fungal pathologies with warm and moist environments (see paragraph [0086]) pointed out by the Examiner and exemplified by the experiment of **Wassenaar** with application by cotton-polypropylene pads. The killing and inhibition of

microorganisms, including fungi, by ACQAs above and beyond inhibition due to a moisture reducing effect was not known in the art and is not obvious in face of any of the cited art.

Applicant respectfully points out that it was not obvious and was entirely unexpected to employ ACQAs as agents to kill and inhibit dermatophytic fungi and bacteria. As shown in the Merck reference cited by the Examiner fungal infections (tinea corporis) can occur at any site on the body. Scalp and nail infections are pointed out as being particularly difficult to treat. Therefore, it is apparent that fungal infections are common on areas of the body that are generally not particularly moist. As demonstrated by Applicant's *in vitro* tests, ACQAs do kill and inhibit fungi (*Trichophyton*, a dermatophytic pathogen mentioned in the reference, was used in those tests). The ability of Applicant's inventive method to kill and inhibit dermatophytic fungal pathogens and bacteria on dry parts of the body would not have been obvious in light of any of the cited prior art. In the Examiner's "Response to Arguments (page 6) the Examiner notes that "fungal infections are cured by antifungal medication." This statement appears a bit inapposite considering that **Wassenaar** very clearly states that the fungal infection was "improved;" there was no suggestion that the infection was in any way cured. One of ordinary skill in the art would understand that the improvement in the fungus infection was attributable to the antiseptic vehicle and the drying (antiperspirant) effect of the treatment. Whereas, the tests reported by Applicant support the effectiveness of ACQA treatments even in situations where excessive moisture is not involved.

Applicant clearly demonstrates the ability of ACQAs to kill both bacteria and dermatophytic fungi apart from any drying effects of these compounds. The prior art was not aware that ACQAs are effective at both killing and inhibiting dermatophytic fungi and bacteria. Applicant's results show that these agents can work in situations where reduction of excess moisture is not necessarily required. This means that the property of reducing excess sweating may enhance the effectiveness of these agents

but is not required for the effectiveness. Faced with the prior art teaching one of ordinary skill in the art would not have expected this.

In view of the foregoing, Applicant respectfully requests the Examiner to withdraw the rejections based on **Wassenaar**. Applicant is desirous of bringing this prosecution to a successful conclusion and will therefore contact the Examiner to schedule an interview prior to the requested examination in response to an RCE. It is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

The Examiner is requested to call the undersigned attorney at the Los Angeles telephone number (310) 229-9928 to discuss any steps that will advance prosecution of this case. You are hereby authorized to charge any fees due and refund any surplus fees to our Deposit Account No. 22-0261. Please reference matter number 94902-256172.

Respectfully submitted,

VENABLE LLP

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Attachment: 21 CFR Part 333 and 369

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